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## **Mortality and preoperative cardiac function in vascular amputees: an N-terminal pro-brain natriuretic peptide (NT-proBNP) pilot study**

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# Mortality and preoperative cardiac function in vascular amputees: an N-terminal pro-brain natriuretic peptide (NT-proBNP) pilot study

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**Objective:** To determine preoperative ventricular function in vascular amputees by measuring N-terminal pro-brain natriuretic peptide (NT-proBNP) and to analyse the relationship between NT-proBNP levels and 30-day postoperative mortality.

**Design:** Prospective pilot study.

**Subjects and methods:** In 19 patients planned for a lower limb amputation for non-reconstructable peripheral arterial disease NT-proBNP was measured the day before amputation.

**Results:** Four amputees died within 30 days after the amputation. In 17 of 19 patients NT-proBNP values were found more than 2 standard deviations above the age corrected reference value. Pre-amputation NT-proBNP levels did not differ significantly between non-survivors and survivors ( $P=0.162$ ).

**Conclusion:** Preoperative NT-proBNP levels are not significantly related to 30-day mortality after lower limb amputation procedure. Preoperative NT-proBNP levels are very high, indicating that serious ventricular dysfunction may be present in vascular amputees.

## Introduction

Peri-operative mortality in lower limb amputees is high.<sup>1</sup> Myocardial infarction is the most common cause of postoperative mortality.<sup>2</sup> Cardiac function is relevant for the postamputation rehabilitation process because energy expenditure during gait is increased in lower limb amputees.<sup>3-5</sup> Thus regaining bipedal gait adds an additional level of stress to the heart that

may already be compromised by pre-existing heart disease. On the basis of the above arguments one should pay attention to the presence of heart disease in vascular amputees to prevent complications (mortality) not only in the peri-operative phase but also in the rehabilitation phase.

Recent literature has shown that plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are elevated in patients with asymptomatic left ventricular systolic dysfunction and NT-proBNP levels are highly accurate for detecting left ventricular failure.<sup>6</sup> Elevated NT-proBNP levels might also be a biomarker for the early diagnosis of right ventricular systolic dysfunction.<sup>7</sup> Congestive heart failure patients

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with NT-proBNP values levels above median had a one-year mortality of 53% compared with 11% in patients with below-median levels of NT-proBNP.<sup>8</sup> In fact NT-proBNP was the strongest independent predictor of one-year mortality in patients with acute coronary syndrome.<sup>9</sup>

The aim of this study was to analyse the relationship between preoperative NT-proBNP levels and 30-day mortality in lower limb amputees who are amputated for a vascular disease.

## Methods and materials

Nineteen consecutive patients undergoing a lower limb amputation were studied; the amputations were transtibial, transfemoral or through-knee. Amputations were performed in the Vascular Surgery Department at the Nij Smellinghe Hospital in Drachten and University Medical Centre Groningen. Patients were included if they underwent the amputation for non-reconstructable peripheral arterial disease. Demographics and cardiac history were retrieved from the patient charts.

EDTA-anticoagulated blood (10 mL) was collected by venous puncture the day before the amputation. Blood samples were centrifuged within 2 hours after sampling. Before storage at  $-80^{\circ}\text{C}$  30  $\mu\text{L}$  of an aprotinin solution (protease inhibitor, 10 000 kIU/mL; Bayer, Germany) per millilitre of plasma was added to the samples. NT-proBNP (electrochemiluminescence immunoassay; Roche Diagnostics) was measured in the week after collection.

Differences in levels of preoperative NT-proBNP between patients who died in the 30-day period after the amputation and patients who survived that period were analysed using Mann–Whitney test. Differences in levels of preoperative NT-proBNP between the patients with different amputations levels were analysed using the Kruskal–Wallis test.

The preoperative NT-proBNP levels in non-survivors and survivors were compared with the reference values given by the manufacturer.

## Results

Nineteen patients, 6 women and 13 men with a mean age of 69.1 (SD 12.5) years, participated in the study, 15 of whom had a history of cardiac disease such as heart failure, valve disorder, myocardial infarction and atrial fibrillation. In total, five transfemoral, four through-knee and 10 transtibial amputations were performed. Four amputees died within 30 days after the amputation. The median interquartile ranges (IQR), mean values and standard deviations of NT-proBNP are summarized in Table 1. In general, levels of NT-proBNP were high. In total 17 of 19 patients (89%) had NT-proBNP value levels more than 2 SDs above the age-corrected reference value. NT-proBNP levels were higher in non-survivors than in survivors but the difference was not significant. NT-proBNP levels were highest in transfemoral amputees but this difference was not significant ( $P=0.248$ ).

**Table 1** NT-proBNP levels (ng/L) for the study population ( $n=19$ ) and for the different subgroups

|                                | Median | IQR         | Mean   | SD     | P-value |
|--------------------------------|--------|-------------|--------|--------|---------|
| NT-proBNP in total study group | 3 723  | 428–6149    | 6 148  | 8 984  |         |
| Survival                       |        |             |        |        | 0.162*  |
| Non-survivors ( $n=4$ )        | 11 761 | 1612–3221   | 15 198 | 16 352 |         |
| Survivors ( $n=15$ )           | 2 471  | 417–5971    | 3 734  | 4 103  |         |
| Level of amputation            |        |             |        |        | 0.248** |
| Transfemoral ( $n=5$ )         | 5 971  | 2069–27 693 | 13 207 | 14 908 |         |
| Through-knee ( $n=4$ )         | 4 477  | 1909–5920   | 4 102  | 2 117  |         |
| Transtibial ( $n=10$ )         | 823    | 381–6388    | 3 437  | 4 842  |         |

NT-proBNP did not differ significantly between non-survivors and survivors and (30 days)\* or between groups with different amputation levels\*\*.

## Discussion

NT-proBNP levels in the amputee non-survivor group were very high compared with those of survivors but the difference was not significant. Preoperative NT-proBNP levels were not associated with the level of amputation. Overall NT-proBNP levels were high in 89% of the vascular amputees, indicating that serious cardiac disease may be present.

These high NT-proBNP levels may have clinical importance because cardiac disease in vascular amputees may be underdiagnosed in the preoperative phase for several reasons. First, 25% of vascular amputees have diabetes, which is associated with a generalized hyposensitivity to pain.<sup>10</sup> Therefore silent ischaemia may be a common phenomenon in diabetic amputees with coronary heart disease. Second, non-ambulant patients with peripheral vascular disease fail to exhibit symptoms of coronary disease because the progressive limb pain limits the ability to attain levels of activity necessary to provoke symptoms of cardiac ischaemia. In the pre-amputation phase obviously most attention will be focused on treatment of the life-threatening ischaemic limb and concomitant heart disease may be overlooked. In contrast, in the rehabilitation phase cardiac problems may arise when the amputee starts walking with a prosthesis and the extra energy necessary for walking with a prosthesis cannot be provided by the compromised heart.<sup>3-5</sup>

NT-proBNP measurements in this study were not significantly related to 30-day mortality. The chosen follow-up of 30 days may be too short. A longer follow-up of one year might show a statistical significant relationship between preoperative NT-proBNP measurements and mortality in amputees.<sup>8,9</sup> In these studies NT-proBNP was an independent prognostic factor of one-year mortality in a different population.<sup>8,9</sup> Because NT-proBNP levels are subject to intra-individual variations these levels may not be accurate enough as the only biomarker to evaluate ventricular function adequately.<sup>11</sup>

The statistical power of this study is limited by the small number of patients included. In a post-hoc sample size calculation, the standard deviation of the population in this study (8984) and the

difference in NT-proBNP between non-survivors and survivors was used. This analysis resulted in a total sample size of 22 patients: 11 in each group. Our total sample was too small and the distribution of non-survivors and survivors was not optimal for statistical analysis. However, the date of the current study can be used for sample size calculation in future research focusing on cardiac disease in vascular amputees.

### Clinical messages

- Preoperative NT-proBNP levels in vascular amputees are not statistically related to 30-day mortality and level of amputation.
- Preoperative NT-proBNP levels in vascular amputees are high, indicating that serious ventricular disease may be present.

### Acknowledgements

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### Competing interests

None declared.

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